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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/754,014	NORDSTROM ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,10,14,51-54,65,67 and 69-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *72* is/are allowed.

6)☒ Claim(s) *5,10,14,51-54,65,67,69-71 and 73-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8 August 2005 has been entered.

Claims 5, 10, 14, 50-55 and 65-76 were considered in the Final Office Action mailed 7 April 2005. Claims 50, 55 and 66 were canceled and claims 5, 10, 14, 51-54, 65, 72, 73 and 76 were amended in the 8 August Paper. Claims 5, 10, 14, 51-54, 65, 67 and 69-76 are pending and under consideration.

Response to Amendment and Arguments

Rejection of claims 50, 55 and 66 is rendered moot by the cancellation thereof.

Specification

Objection to the specification under 35 U.S.C. 132 for the reasons set forth in the previous Office Action is **maintained in part** and **withdrawn in part**.

In the previous Office Action it was determined that the amendment filed 28 January 2005, and Sequence Listing and CRF filed 18 August 2004 introduce new matter into the disclosure.

In response, Applicant has amended the paragraph from page 31, line 29 through page 32, line 12 to correct the typographical error in the sequence CAGGTAAGT and to remove the recitation of subsequences within the specifically disclosed sequence.

The specification was also objected to because, the sequences added to the paragraph from page 33, line 13 through line 24 and to the sequence listing as SEQ ID NO: 18 and 19 constitute new matter.

In response to the *prima facie* case set forth on page 3 of the previous Office Action, Applicant contends that the sequences are supported by the teachings at page 33, lines 13-20, which Applicant asserts, "teaches a consensus 3' splice site sequence Y_{11}NYAGG, which can be modified by extending the polypyrimidine tract Y_{11} to 16 bases. Accordingly, the new sequence becomes Y_{16}NYAGG (SEQ ID NO: 18)" and "[t]he specification also teaches that the 3'splice site consensus sequence can be modified by having the 16 base polypyrimidine tract include 7 consecutive T residues as shown in intron OPTIVIS 8" (page 8 of the 8 August Paper).

These arguments have been fully considered but are not deemed persuasive. The passage from the specification cited by Applicant, as originally filed, reads as follows (emphasis added):

> The sequence of the 3' splice site (3' ss) matches the established consensus sequence, Y_{11}NYAG↓G, where Y=C or T, and N=any base. In 3' splice sites the polypyrimidine tract (Y_{11}) is the major determinant of splice site strength. For optimal splice site function in OPTIVS8B, the length of the polypyrimidine tract was extended to 16 bases, and its sequence was adjusted to contain 7 consecutive T residues.

As discussed in the previous Office Action, the paragraph sets forth a generic consensus sequence Y_{11}NYAG↓G and then describes the OPTIVS8 intron which comprises the sequence set forth as SEQ ID NO: 13. The specification does not explicitly contemplate a genus

comprising the sequence Y_{16}NYAG↓G or comprising the sequence TTCTTTTTTTCTCTTCNYAG↓G and does not contemplate any species within the genus other than OPTIVS8. Therefore, the sequences Y_{16}NYAG↓G and TTCTTTTTTTCTCTTCNYAG↓G find neither explicit nor implicit support in the originally filed application.

Claim Objections

Objection to claim 51 as containing informalities is **withdrawn** in view of the amendments thereto.

Claim Rejections - 35 USC § 112

Claims 5, 10, 14, 51-54, 65-71 and 73-76 **stand rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter. Pages 5-7 of the previous Office Action set forth various grounds for rejection. As will be discussed in detail herein below, some amendments to the claims overcome some grounds for rejection while other claims are amended such that they newly comprise subject matter previously identified as new matter. In the latter case, the rejections set forth in the previous Office Action are newly applied to the amended claims.

The previous Office Action first contends that amended claims 5, 10 and 14, and claims 50-55 as they depend from claims 5, 10 or 14, contain new matter because the newly added phrase "having a sequence of", requires only that the sequence identified comprise some

sequence within the defined sequence while the original disclosure required that the identified splice site and branch point sequences comprise the entirety of the defined sequence. As stated in the Office Action, as the originally filed disclosure did not contemplate genera of 5' and 3' splice sites and branch points comprising all possible sequence combinations within the sequences CAGGTAAGT, TACTAAC and TTCTTTTTTTCTCTTCACAGG the claims as amended embrace new matter.

In response, Applicant contends that the claims have been amended to recite a plasmid containing one or more synthetic intron having "the sequence of" the disclosed splice sites and branch point. However, in fact, the claims still recite the phrase "a sequence of" and therefore still comprise the subject matter identified as new matter. In addition, claim 65 and 76 have been amended to recite the phrase "a sequence of" such that this rejection now applies to claims 65, 67, 69-71 and 76. Amending the claims to recite "the sequence of" rather than "a sequence of" would overcome this ground for rejection.

Next, claims 52 and 53 were rejected because the originally filed disclosure does not suggest an embodiment wherein the strength of the "alternative 3' splice site" is weakened with respect to the first 3' splice site or wherein the sequence modification produces any sequence other than 5'-CTTTAAATC-3'.

In response, Applicant has amended the claims such that they are limited to the embodiment wherein the 3' splice site is weakened with respect to the alternative splice site, which addresses the first ground for rejection. However, the claims still encompass embodiments wherein the strength of the 3' splice site is weakened by changing any three consecutive T's to

A's (*i.e.*, the sequence modification produces sequences other than 5'-CTTTAAATC-3'). Applicant's remarks do not address this ground for rejection.

Claim 65-71 and 73 were further rejected in being directed to a synthetic transcription unit comprising the generic sequence Y_{16}NYAGG and claim 67 was further rejected in being directed to a synthetic transcription unit comprising the sequence TTCTTTTTTTCTCTTCNYAGG (SEQ ID NO: 19), which sequences are not supported by the originally filed disclosure. Applicant's remarks with regard to support for the sequences are the same as those addressed herein above in response to the objection to the specification under 35 U.S.C. 132. In brief, Applicant contends that the sequences are supported by the teachings at page 33, lines 13-20, which Applicant asserts, "teaches a consensus 3' splice site sequence Y_{11}NYAGG, which can be modified by extending the polypyrimidine tract Y_{11} to 16 bases. Accordingly, the new sequence becomes Y_{16}NYAGG (SEQ ID NO: 18)" and "[t]he specification also teaches that the 3'splice site consensus sequence can be modified by having the 16 base polypyrimidine tract include 7 consecutive T residues as shown in intron OPTIVIS 8" (page 8 of the 8 August Paper).

These arguments have been fully considered but are not deemed persuasive because the passage from the specification cited by Applicant sets forth a generic consensus sequence Y_{11}NYAG↓G and then describes the OPTIVS8 intron which comprises the sequence set forth as SEQ ID NO: 13. The specification does not explicitly contemplate a genus comprising the sequence Y_{16}NYAG↓G or comprising the sequence TTCTTTTTTTCTCTTCNYAG↓G and does not contemplate any species within the genus other than OPTIVS8. Therefore, the

sequences Y_{16}NYAG↓G and TTCTTTTTTTCTCTTCNYAG↓G find neither explicit nor implicit support in the originally filed application.

Claims 65-71 were also rejected because the specification does not teach a genus of synthetic transcription units comprising the combination MAGGTRAGT...YNYTRAY... Y_{16}NYAGG as claimed. In response, Applicant has amended claim 65 such that the 5' splice site is limited to comprising SEQ ID NO: 15 and the branch point is limited to comprising SEQ ID NO: 17, which adequately addresses this ground for rejection.

Claims 73-75 were also rejected in being limited to comprising a synthetic intron from about 90 to 200 nucleotides in length. The previous Office Action contends that the originally filed specification does not contemplate a synthetic intron having a range of 90 to 200 nucleotides in length. Instead, the specification, in the paragraph bridging pages 33-34, teaches that "most naturally occurring introns are 90-200 nt in length" and that the synthetic intron disclosed in the instant application, which is 118 nts, falls within this range. The specification does not support a synthetic intron limited to a size other than 118 nucleotides.

In response, Applicant cites the same teachings from the specification that are cited in the Office Action and asserts that the skilled artisan would recognize that the specification is explicitly and/or implicitly teaching a synthetic intron with a length of 90-200 nucleotides.

This argument has been fully considered but is not deemed persuasive. In the original disclosure, the range presently recited in the claim is recited only in reference to the length of most naturally occurring introns. There is no explicit teaching of synthetic introns 90-200 nt in

length, other than the single species of 118 nt, and the teaching does not suggest that the size of synthetic introns should be constrained to a size range of 90-200 nt in length. Therefore, the limitation of a synthetic intron to a size range of 90-200 nt, as presently claimed, is neither explicitly nor implicitly supported by the disclosure as originally filed.

Finally, the previous Office Action contends that the limitation of the branch point to being located within the range of 24 to 38 nucleotides upstream from a site of splicing in the 3' splice site in claims 70 and 75 constitutes new matter because the specification teaches only that, in mammals, "[t]he branch point is typically located 18-38 nts upstream of the 3' splice site" and that the branch point in OPTVS8 is located 24 nts upstream from the 3' splice site. There is no disclosure of a synthetic intron comprising a branch point generically limited to being located within the range of 24-38 nts upstream of a 3' splice site as recited in the instant claims. Therefore, the limitation constitutes new matter.

In response, Applicant asserts that based on the passage cited in the Office Action the skilled artisan would readily recognize that the specification is explicitly and/or implicitly teaching a branch point located in the range of 18-38 nucleotides upstream of a 3' splice site.

This argument is not persuasive because, first, the claims are not limited to a branch point located in the range of 18-38 nucleotides upstream of a 3' splice site. Instead the claims recite a range of "24-38". There is clearly no support for a range with a lower limit of 24 in the originally filed disclosure. Furthermore, even if the claims did recite a range of 18-38, the limitation of a synthetic transcription unit to comprising to a branch point located in the range of 18-38 nucleotides upstream of a 3' splice site is not supported. The passage cited in the previous Office

Action (bridging pages 32-33 of the specification) discloses 18-38 nt upstream of the 3' splice site as a typical location for a branch point sequence. However, there is no explicit teaching of a synthetic intron comprising a branch point located in the range of 18-38 nucleotides upstream of a 3' splice site, other than the single species of 24 nt, and the teachings of the specification do not suggest that the location of branch points in synthetic introns should be constrained to 18-38 nt upstream of the 3' splice site. Therefore, the limitation is neither explicitly nor implicitly supported by the disclosure as originally filed.

Claim Rejections - 35 USC § 103

Claims 5 **stands** rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Mascarenhas (IDS #CS) or Petitclerc (1995) *J. Biotechnol* 40:169-178 in view of any one of Mulvihill et al. (IDS #AC), Carrano et al. (IDS AD) or Ligon et al. (IDS AE).

As stated in the previous Office Action, "although the art was not previously applied to claims 5-7, which limited the splice sites and branch points to comprising specific sequence, the newly amended claims require only that the splice sites or branch point comprise a sequence of the sequences set forth (*i.e.*, any two or more contiguous nucleotides; *Id.*). Although the art does not disclose a specific sequence for the branch point and splice sites, the instant application teaches that mammalian intronic splice sites and branch points comprise conserved sequences (see especially the discussion on page 32 and 33). Therefore, the skilled artisan would expect that the intron of the prior art references would comprise at least two contiguous nucleotides present in one of the sequences set forth in the instant claims. Therefore, the claimed invention as

a whole would have been obvious to one of ordinary skill in the art at the time the invention was made" (emphasis added).

Claim 10 **stands** rejected and claims 51 is **newly rejected** under 35 U.S.C. 103(a) as being unpatentable over Mascarenhas or Petitclerc in view of Mulvihill, Carrano or Ligon, as applied to clam 1 above and in further view of Zitvogel (IDS CQ).

As stated in the previous Office Action, although the art was not previously applied to claims 10-12, which limited the splice sites and branch points to comprising specific sequence, the newly amended claims require only that the splice sites or branch point comprise a sequence of the sequences set forth (*i.e.*, any two or more contiguous nucleotides; *Id.*). Although the art does not disclose a specific sequence for the branch point and splice sites, the instant application teaches that mammalian intronic splice sites and branch points comprise conserved sequences (see especially the discussion on page 32 and 33). Therefore, the skilled artisan would expect that the intron of the prior art references would comprise at least two contiguous nucleotides present in the sequences set forth in the instant claims. Therefore, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claim 51, which was previously limited to having "the sequence of SEQ ID NO: 10, RESIDUES 1-9, is presently amended to recite that the intron comprises "a sequence of residues 102-122 of SEQ ID NO: 13". Thus, the scope of claim 51 has been expanded to encompass a 3' spice site and alternative spice site having any two or more contiguous residues within the

sequence set forth as SEQ ID NO: 13. Therefore, the art applies to claim 51 for the same reasons as those set forth with regard to claim 10.

Claim 14 **stands** rejected under 35 U.S.C. 103(a) as being unpatentable over Dirks et al. (IDS #CT) in view of Rautmann and Breathnach (1985) *Nature* 315:169-178.

As stated in the previous Office Action, although the art was not previously applied to claims 5-7, which limited the splice sites and branch points to comprising specific sequence, the newly amended claims require only that the splice sites or branch point comprise a sequence of the sequences set forth (*i.e.*, any two or more contiguous nucleotides; *Id.*). Dirks teaches a 5' splice site comprising the sequence "GG" a branch point comprising the sequence "AC" and a 3' splice site comprising the sequence "AG" according to the limitations of the instant claim (see especially Figure 1 and the caption thereto). Therefore, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

In response to the *prima facie* case, Applicant contends that the art does not apply to the claims because the sequence comprised by the intron used in the art is not the same as the sequences to which the instant claims are limited. This argument has been fully considered but is not deemed persuasive. As pointed out in the previous Office Action, the claims, as written, do not limit the structures recited therein to comprising the entire sequence set forth in the referenced SEQ ID NO because they require only that a sequence thereof be comprised. The evidence submitted by Applicant confirms that the introns do comprise a sequence of the

sequences recited in the claims. For example the ZMADH1SA sequence cited on page 11 of the Remarks comprises a 5' splice site comprising the sequences "aa", "ag" and "gt" which sequences are also comprised within residues 1-9 of SEQ ID NO: 13. Furthermore, the ZMADH1SA sequence comprises a branch point comprising the sequence "aa", which sequence is comprised within residues 93-99 of SEQ ID NO: 13, and a 3' splice site comprising the sequence "ca", which sequence is comprised within residues 102-122 of SEQ ID NO: 13. Thus, the art does teach constructs comprising a sequence of the SEQ ID NO's recited in the claims. It is noted that Applicant's arguments would be persuasive if the claims were amended to recite "the sequence of SEQ ID NO" rather than "a sequence of SEQ ID NO" wherever it occurs.

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 65, 70, 71 and 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The MPEP states, "[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*,

650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." (MPEP § 2163.06). The MPEP further states, "[w]henever the issue arises, the fundamental factual inquire is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in the application" (*Id.*, § 2163.02). The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

Claim 18 has been amended to recite, "a 3' splice site having a sequence of SEQ ID NO: 18, wherein the 3' splice site contains 7 consecutive T residues" and claim 73, which was newly added in the amendment filed 28 January 2005 recites, "a 3' splice site having a sequence Y_{16}NYAGG wherein Y=C or T and contains 7 consecutive T residues". The 3' splice site of the claims is thus generic to any sequence comprising Y_{16}NYAGG and 7 consecutive T residues, wherein the consecutive T residues might be anywhere within the sequence. The disclosure as filed does not disclose a genus as recited in the claims. Instead, the disclosure sets forth a single species wherein the 3' splice site comprises the sequence TTCTTTTTTTCTCTTCACAGG (*e.g.*, at page 32). As there is nothing in the disclosure that would lead the skilled artisan to the generic structure presently claimed (*i.e.*, wherein the 7 consecutive T residues can be anywhere in generic sequence), the generic limitation constitutes new matter.

Allowable Subject Matter

Claim 72 is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER